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# THE N.V. ORGANON PHARMACEUTICAL FACTORY



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COMBINED INTELLIGENCE OBJECTIVES
SUB-COMMITTEE

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# THE N.V. ORGANON PHARMACEUTICAL FACTORY OSS, HOLLAND

Report by

Lt. Colonel H.J. PHELPS

CIOS Black List Item 24
Medical

COMBINED INTELLIGENCE OBJECTIVES SUB COMMITTEE
G-2 DIVISION, SHAEF (Rear) APO 413

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# I. VISIT TO N.V. ORGANON at OSS - HOLLAND

## Target No. 24/21

The Organon pharmaceuticals factory at Oss was visited on November 3rd, 9th, 10th and 11th, 1944. My first visit confirmed our suspicions that this factory had been under the control of Schering of Berlin throughout most of the occupational period, and had been an important centre of manufacture of this concern after the bombing of their plants in the Berlin area. It was also apparent that the Germans had left Oss in a panic and had left all the installations and many records behind. I had the most amazing co-operation from Dr. Tausk, Managing Director of the plant, who mobilised the whole of his high level technical staff to assist me by sorting and translating available information on the more important items of manufacture. I then spent two days in discussing the material available with Dr. Tausk and his various specialists, the Organon Company providing the services of an English-speaking stenographer who took notes on these discussions which form the basis of the technical appendices to the present report.

History of the Organon Factory during the Occupation:

The Organon Factory lies a little to the east of Oss railway station, adjacent to the Van Zwanenberg meat packing factory (from which Organon obtained supplies of animal glands for extraction) and the Hartog margarine plant, the three factories forming what is virtually one industrial complex.

The directors of the company left Oss the day after the German invasion of Holland in an attempt to reach England with important technical information and considerable stocks of some rarer drugs, particularly insulin. The party became separated and although two of the Dutch directors and an English manager, who was visiting the factory at the time, eventually reached England, Dr. Tausk was unable to do so. He returned to Oss on the 15th May 1940 and for some time neither he nor the company were interfered with by the Germans,

although the controlling interest of the Organon factory appears to lie with the Van Zwanenberg combine, in which there is a large Jewish interest. In November 1940 the occupying authorities declared the Organon concern to be confiscated as a Jewish business and the shares were vested in a German trading company which had been set up in Holland to act as a receiver and custodian of Jewish property. Dr. Tausk was dismissed from the position of Managing Director, but when he applied shortly afterwards in his own name for the position of Director of Laboratories he was promptly engaged and filled this position throughout the occupation. A Dr. Duden of the Schering Company was appointed Trustee of the Organon factory. Dr. Duden was not a technical man and interfered very little in the operations of the factory which continued with its pre-war activities but on a greatly reduced scale.

Early in 1942 the Schering concern formally took over Organon N.V. by purchasing the shares which had been sequested by the German trading company acting as Custodian for Jewish property. From this time the factory was worked entirely as a Schering concern, and a Dr. Zastrow, one of the leading chemists of Schering A.G., came to Oss as technical director of the factory. Schering began immediately to enlarge the factory and to install new plant. New buildings were erected and the staff was increased. In the R.A.F. attacks on Berlin in February 1944 Schering's offices, laboratories, and tabletting and ampouling plants, were entirely destroyed, and much of the other manufacturing capacity severely damaged. In consequence Schering transferred a considerable part of their manufacturing activities to Oss and the enlargement of the factory was accelerated. The installation of new plant at Oss continued without a break during the early days of the Allied landing on the Continent, and work was actually proceeding on the equipment of a new building up to the 4th September 1944. On this day the B.B.C. broadcast a false rumour that the British Forces advancing from Brussels had reached Breda. The Germans in the Organon factory and all German civilians in Oss, left the town in a panic and never returned, although British forces did not reach Oss until the airborne invasion of 17th September.

The chief activity of the Schering Company at Oss centred on the manufacture of hormone preparations. The production of insulin, which was normally one of the principal activities of the Organon factory, was continued on a reduced scale but large quantities of oesterone were made by a new synthetic method devised by Schering, while the production of cortisterone and testosterone was also pushed forward and new technical methods were employed. A new method of the synthesis of Vitamin C was introduced and research on the production of a synthetic Vitamin A was carried to the point of producing a synthetic chemical with about one-tenth of the biological activity of natural vitamin A. A considerable amount of work was also done on the preparation of a synthetic plasma substitute known as Capain, which can now be made on a commercial scale and which appears to have given most satisfactory results in treatment.

The Schering Company was engaged in active research on penicillin, but this work was not carried out at Oss. From information which the Dutch technical people at Oss had obtained from the Germans, it is apparent that Schering had not had much success with this work. On the other hand, the Dutch experts at Oss, and particularly Dr. Tausk, had been able to carry out some research secretly on pencillin and had discovered a strain of moulds which gave a high yield of very active antibacterial substance. It is not as yet certain whether this substance is identical with penicillin. The important cultures are now believed to be held by Professor Julius of Utrecht and when this town is liberated it would seem important to contact Professor Julius and obtain from him a sample of the mould which had been used.

Throughout the occupational period the staff of the Organon factory appear to have been very active in the resistance movement, and many of them certainly displayed remarkable courage. Two of the Organon technical managers were, unfortunately, arrested for their activities. Dr. Boerrigter, who was a most courageous leader of the resistance group, was arrested in 1941 and sentenced to twelve years imprisonment by the local military court. This sentence was, however, referred back to the local Summary court by Berlin and commuted by them to the death sentence.

Dr. Boerrigter was executed in 1942. At the same time Dr. Geerling was sentenced to four years imprisonment and is still in Germany.

Technical Information

The chief points of technical information which were obtained from the records left in the factory, and from the personal knowledge of the Dutch technical staff, were the following:- (technical details are set out in appendices to this report, numbered as shown below).

1. New developments in the commercial preparation of synthetic hormones. (Appendix I).

2. The preparation and use of plasma substitutes.

These were of two types:-

(a) An entirely synthetic substitute for blood liquid which was a colloidal polymer of polyvinyl-pyrrolidon, known by the Germans as PERISTON (Appendix II).

(b) A colloid polypeptide prepared from casein and known as CAPAIN (Appendix III) which appears to be quite free from any toxic effects and which may be regarded as a complete protein substitute. Full details for the manufacture of this substance were obtained.

3. New Developments in Vitamin Chemistry. A new method for the preparation of Vitamin C has been evolved which avoids the use of potessium permanganate and of large quantities of acetone, both of which substances were in short supply in Germany. The new process also evades the existing patents on the production of synthetic Vitamin C. It is, however, admitted that the yield of vitamin is less good than that obtained by the standard process of manufacture (Appendix IV). Research on the production of synthetic Vitamin A was prompted by the fact that supplies of Vitamin A were deficient in Germany. So far these researches have succeeded in producing a substance with about one-tenth of the biological activity of natural Vitamin A, but prospects for the full synthesis of Vitamin A appear to be good. (Appendix V.)

4. Marfanil and Sulpha Drugs. The Germans have done a great deal of work on the preparation and use of MARFANIL and a similar compound known as TIBATIN. Methods for the quantity production of Marfanil have been worked out, and it appears to have been used particularly in association with sulphanilamide. There appeared to be no evidence of the use of Marfaril and pencillin in combination, but this may be due to the fact that the Germans have not apparently succeeded in preparing penicillin in considerable quantity. (Appendix VI). No other significant developments in sulpha drugs were apparent, sulphanilamide and sulphathiazol being the drugs most commonly used.

5. Synthetic Substitutes for Morphine. It was confirmed that the Germans were preparing considerable quantities of DOLANTIN, and this substance could in fact be purchased in many stores in Belgium and Holland. Since the preparation of Dolantin is known in the U.K. and the U.S.A., information was collected only on the applications of Dolantin and on the question as to whether or not the drug causes addiction. (Appendix VII).

6. Anti-louse Powders. The only insecticide in which the experts at Oss knew the Germans to be interested was GESAROL. This substance is almost certainly less effective than D.D.T., and no information was collected on its methods of preparation, which are in any case generally known. A short note on the toxicity of Gesarol was prepared. (Appendix VIII).

7. Penicillin and Anti-bacterial Substances extracted from Moulds. The Germans, and particularly Schering, has carried out intensive research on Penicillin, and had obtained strains of Penicillium notatum from Professor Westerdijk, who has in her laboratories what is believed to be the largest collection of moulds in the world. Apparently, however, the particular strain of penicillium notatum which Professor Westerdijk delivered to Schering was remarkably inactive as regards penicillin formation. Whether this strange circumstance was an accident or due to remarkable ingenuity on the part of Professor Westerdijk could not be ascertained with certainty, as the Organon technicians preferred to keep a discreet silence on the matter, but it was admitted

that Professor Westerdijk had very active penicillin containing cultures on which she had done considerable secret research in association with Professor Julius of Utrecht and Dr. Tausk of Organon. (Appendix IX).

8. Anti-Malarials. No information was available at the Organon factory regarding any new developments in the manufacture of synthetic anti-malarials. Dr. Tausk was of the opinion that there had been no advances on atebrin and plasmoquin, and that there had been no changes in the methods used to prepare these substances. It was confirmed that there had been an increase in the use of the total mixed alkaloids of cinchona instead of refined quinine in the treatment of malaria in order to conserve as far as possible stocks of bark.

9. Dr. Tausk prepared for me a list of chemicals and chemical apparatus which were in short supply during the occupation, with comments specifically on the experiences of the Organon factory (Appendix X.). I also attach a note on the stocks of raw materials of various products and the requirements for the restarting of manufacture in various branches of the factory as at the time of my visit. (Table I following Section II). This information was also handed to the local civil affairs authorities who had passed it to 30 Corps, S.C.A.O., under reference CA/504/I - 3.

H.J.PHELPS.Lt.Col.
E.A.B.6(d).

## II. Discussions with Dr. Lenz, of Organon N.V. Oss.

In the course of my stay at Oss I had the opportunity of several discussions with Dr. Lenz, Director of the Chemical Departments of Organon N.V., who was employed in the Dutch Chemical Warfare Service in 1940. The following is a brief summary of the information given by him :-

Immediately after the occupation of Holland, the Germans examined the Dutch chemical warfare laboratories at Delft, but although all the records had been destroyed the Dutch technicians were asked very few questions. Practically all the Dutch technicians were allowed to depart, or were dismissed, and a limited amount of research was continued, mainly by Germans, on the penetration of vesicants through different types of protective clothing. The people working in these laboratories were interested both in mustard and in "nitrogen mustard". The Germans were plainly interested both in protective clothing against "nitrogen mustard" and in finding a suitable decontaminant. During the latter part of 1940 and early 1941 they did not seem to have had much success.in either direction. It is of interest that the German standard for protective clothing against both vesicants was only two hours' protection. Most of the experiments were carried out on various types of canvas cloth coated with rubber on both sides. 50% of the samples of this kind of material failed to give two hours' protection against ordinary mustard.

In the Spring of 1941 all work in the Dutch laboratories was suddenly suspended and the laboratories, including the remaining Dutch technicians of the laboratory assistant grades, were leased to the Delft Technical High School and used as ordinary teaching and research chemical laboratories. So far as Dr. Lenz was aware, no further work on chemical warfare was carried out.

Although no specific work on gas masks was carried out by the Germans at Delft, Dr. Lenz knew that the Germans were somewhat concerned at the high breathing resistance shown by the G.M.40.

Throughout the occupation period the German troops of all ranks, and uniformed female auxiliaries, in Oss invariably carried gas masks and Losantin tablets even when off duty in the town.

After the middle of 1941 there was practically no pressure on the local Dutch population to obtain gas masks or to undertake any form of anti-gas precautions or exercises. The Dutch State Railways continued to give considerable attention to the problems and their employees were provided with gas masks and instructed in their use. The State Railways also had gas decontamination cars at every major railway station. These cars were, however, either constructed in 1939 or replicas of a type introduced at that time. Dr. Lenz thought that these activities were an independant effort on the part of the Dutch State Railways rather than the result of German pressure or encouragement.

Dr. Lenz knew nothing of any C/W activities by Schering A.G., although this company had taken over Organon factories. This, however, cannot be taken as proof that Scherings are not manufacturing C/W material in German since they were very reticient regarding most of their activities in their home country. Dr. Lenz deduced that Schering were doing a certain amount of physiological research on C/W since he knew that their physiologists had found that rats less than ten days old give no local reaction with "H". After this age a normal local reaction is shown.

The only specific C/W activities by the Germans in Holland, of which Dr. Lenz had any knowledge, were the use of a few ten-litre bottles of arsine which were dropped from an aeroplane in the neighbourhood of Greebe in daylight on 11th May 1940. I questioned Dr. Lenz closely on this event, and he was quite sure that it had occurred and said that some of these containers had been sent to the Dutch C/W laboratory at Delft for examination. This experiment in C/W apparently caused no harm to anybody and was never repeated. In 1943 the Germans took over a large laundry at Ubbergen, near Nijmegen, in order to convert it to a clothing decontamination centre. A small gas testing laboratory was also set up at this laundry.

No other information regarding German C/W activities in Holland could be ascertained from Dr. Lenz or any other organisation in Holland.

Table 1. Requirements for Restarting of Production

| Name of the preparation | Prod.capac. per week. | Raw materials sufficient for | labourers (men or women) | Higher staff | kg of coal daily required in the form of steam | electr. | refrig. | gas per day | Other requirements |
|---|---|---|---|---|---|---|---|---|---|
| 1.Sulfanilamid or | 40 kg p.w. | 40 weeks | 3 | 1 | 200 | | | | per week 80 kg of ammonia (for nr.2) |
| 2.Sulfapyridin | 60 kg p.w. | | 6 | 2 | 250 | 25 | | 120 $m^3$ | and from the 10th we 600kg chlor sulfonacid and 400l. of benzol (weekly) |
| 3.Liverextr. (Pernaemon) | 6000kg liver p.w. | 3 weeks | 12 | 1 | 900 | 100 | 250 | | |
| 4.Vitamin D | 40 a 50 g | 6-7 weeks | 1 | 2 | 20 | 50 | | | |
| 5.Vitamin C | 15 kg | 26 weeks | 9 | 2 | 500 | 150 | | | Methanol and NaOH to be stated later on |
| 6.Cholesterol(semi-manuf.) | 6000kg raw material | 1 week | 4 | | 600 | 100 | | | |
| 7.Nicotinic-acid | 700 g | more than 1 year | 1 | 1 | 25 | | | 25 $m^3$ | |
| 8.Filling of all kinds of ampoules | | | 45 (girls) | 2 | 100 | 160 | | 10 $m^3$ | |
| 9.Pharmaceut packing | | | 30 (girls) | 2 | 150 | | | | |
| 10.Production of tablets | 3 3½ mill | | | | | | | | |
| 11.Manufacture of coated tabl. | | | 7 | 1 | 50 | 60 | | | |

The capacity of the Departments, mentioned under numbers 8, 9, 10 and 11, allows filling, production of tablets and packing in charge of third parties.

## APPENDIX I.

### SCIENTIFIC AND TECHNICAL DEVELOPMENTS IN THE PREPARATION OF SYNTHETIC HORMONES

Oxidation of Cholesterol:

The oxidation of cholesterol-acetate dibromide is at present carried out in a homogeneous mixture of acetic acid and ethylenedichloride.

The result of this new procedure is a 50% increased yield. This method is applied now by Ciba (Basle), Schering (Berlin) and Organon.

Desoxycorticosterone-acetate:

The preparation of diazomethane is now possible on a relatively large scale, and in consequence it is possible to prepare desoxycorticosterone-acetate on a technical scale. There are no fundamental changes from the original Reichstein procedure for the synthesis.

Progesterone:

As the new oxidation-process of cholesterol (see above) gives no pregnenolone-acetate, it was necessary to look out for a new preparation method for this substance. In the Schering works the procedure (which has been published by Butenandt c.s. in Berichte) has started on a technical scale. With this method it is possible to reach a 33% yield of progesterone from Dehydro androsterone-acetate.

Ethinyl-testosterone:

The preparation of ethinyl-androstenediol is now possible with other alcohols than tertiary butanol.

Synthetic Oestrone:

It was very important for Schering to prepare oestrone from another source than pregnant mares' urine.

The chemists of Schering, especially Inhoffen, have carried out the synthesis of oestrone starting from dehydro androsterone-acetate and as far as we know this procedure has been applied on a technical scale, (published in Berichte by Inhoffen).

The most difficult stage is the dehydrogenating and demethylating of the first ring. Following the data received from the German chemists the total yield is between 10 and 20%.

As far as is known the whole procedure is not yet carried out regularly in the factory.

## APPENDIX II.

## PERISTON.

This substitute for blood liquid was prepared by Weese and Hecht (pharmacological institute of the I.G. Farben), described in the publication : Hecht und Weese "Periston, ein neuer Blutflüssigkeitersatz" (Münch. med. Wschr. 90, 11 (1943) No.1.

It consists of a colloid, the polymerisation product polyvinylpyrrolidon (known as "Kollidón") in a 2.5% solution, to which is added 0.9% NaCl, 0,9042% KCl, 0,025% $CaCl_2$, 0,0005% $MgCl_2$, 0,0024% $NaHCO_3$ and ca. 10 vol. % free $CO_2$. This solution has a pH 6, and after being sterilized is ready for use and keeps indefinitely. This product and similar mixtures of slightly different composition are described collectively as "Periston". In the animal it normalizes the blood pressure after an acute loss of blood. Its action persists for one or two days; after three to four weeks the substance can no longer be detected in the blood.

Clinical experiences were published by Klees (Münch. Med. Wschr. 90, 29 (1943) No.2. According to this author Periston is superior to all other known plasma substitutes. He tested it in 50 cases of haemorrhage - mostly severe - (laparotomies, various obstetrical cases); the doses varied from 100 to 700 $cm^3$. He observed a prompt restoration of normal blood pressure without noxious influences. The main actions are:-

(1) An analeptic action;

(2) A vasotonic action;

(3) An improvement of the capillary circulation.

Dieckhoff and Künstler (Dtsch. Med. Wschr. 69, 589 (1943) No.33/34, obtained favourable results with Periston in alimentary intoxication of sucklings.

Fonio "Blutersatz im Felde" (Sitz. ber. mediz. Bezirksverein, Bern-Stadt, Schweiz. med. Wschr. 73, 1416 (1943) No.47, remarks, concerning "das an der Ostfront verwendete Periston": "Die Akten über die Wirkung desselben sind noch nicht abgeschlossen; Armeepathologen machen auf Leber-Nierenschädigungen aufmerksam".

The last work has not yet been said about its action; German army pathologists have called attention to liver and kidney damage.

## APPENDIX III.

## APPLICATION OF CAPAIN IN SHOCK.

Literature: L.A.G. Hissink, Ned. Tijdschr. v. Geneesk. 88, 521 (1944); 88, 824 (1944).
J.H.P. Jonxis, Maandschr. Kindergew. 13, 169 (1944)

Capain is an aqueous solution of the breakdown products of casein, obtained by the action of papain on this protein. It is characterised by its high colloidosmotic pressure and its freedom from anaphylactogenic properties. It serves to retain fluid in the blood stream and also provides readily assimilable nitrogen to the body.

It has been issued for clinical purposes in 100 cc. ampoules filled with a 15% solution of the combination of these peptones and polypeptides.

A special type of capain is prepared for intravenous nitrogen feeding especially for infants. The source of protein in this case consists of two parts of casein and one part of lactalbumen, to supply the necessary amount of tryptophane and cystein.

Method of Application:

The usual dose of capain is from 75 to 150 cc. diluted with physiological saline, or 5% glucose solution to 1 L. It is injected intravenously, the rate of the injection depending on the condition of the patient.

In cases of shock, blood pressure is chosen as the criterion, severe cases demanding a faster rate amounting up to 1 L per hour.

Results.

A review is given of twenty cases of more or less severe shock. The results of the treatment were satisfactory; only three of the patients died in the first week after the transfusion. Five of the patients had a slight general reaction (shivers).

With another twenty patients the author claims to have obtained similar favourable results, but no details are given.

Jonxis claims favourable results in infant feeding by the intravenous route. It is well tolerated and he gains the impression that capain is a complete protein substitute.

Method of Preparation

The following prescription is based on information obtained from Professor Brinkman of Groningen, who is the inventor of capain, and on limited experience in the Organon factory.

120 grs of sodium caseinate (soluble) are dissolved in 900 cc. of cold water. To this solution is added a buffer solution of the composition:

40 vol. of citric acid 21 gr/l.
60 vol. of alkaline sodium phosphate ($Na_2HPO_4$ 2 aq) 35,6 gr/l.

To this mixture 900 cc. of boiling water and finally 12 gr of papain (1 : 80) are added. The cloudy solution is stirred for ten hours at a temperature of 60 to 70° C. The initial pH of the salution is approximately 5.8. During the digestion much of the casein dissolves but the cloudiness does not disappear completely. The solution is left overnight and a precipitate of undigested material settles to the bottom. It is decanted or filtered. To the filtrate trichloro-acetic-acid is added to a final concentration of 3 g/100 cc. The precipitate is filtered off through folded filters and the clear filtrate neutralised with 25% NaOH until just red to Congo red. At this acidity the trichlore-acetic-acid is transformed into chloroform and sodium carbonate, provided the temperature is not too low. It is found advantageous to keep the solution at 60 to 70° C to promote the reaction. In case the solution becomes alkaline it is neutralised by means of citric acid.

The solution is then concentrated in vacuo to one-third of its original volume. The temperature in the original recipe was not specified but apparently 60 to 70° C will do. At the end of the process the temperature is raised to boiling point for a few minutes. Finally the solution is kept for two to three days at room temperature. A slight precipitate which occasionally forms is filtered off through asbestos fibre or hyflo filters.

## APPENDIX III (Continued)

The nitrogen content of the filtrate is estimated. The strength of the solution is calculated by taking 8 x the N-content. It is adjusted to 13 to 14%, calculated back to protein. As a preservative 2% nipagin (p-oxy-benzoicacid methylester) is added.

It is issued in 100 cc. ampoules. Before use these ampoules must be carefully cleaned, preferably by bichromate-sulphuric acid solution, followed by frequent washings with water. The last rinse should always be one of freshly distilled apyrogenic water. The filled ampoules are sterilized for one hour by live steam.

Samples of the ampoules ready for issue are subjected to a sterility test.

The toxicity in test animals is quite low; 5 cc are well tolerated if slowly injected in the marginal earvein of a rabbit. No anaphylactic reactions are apparent in appropriate test on guinea pigs. Organon have so far prepared two batches only and the definite tests for the toxicity have not yet been established. Meanwhile the above-mentioned tests are used provisionally. Care should be taken to avoid the development of micro-organisms during any stage of the process as subsequent sterilisation would still leave dead bacterias in the solution liable to cause pyrogenic reactions.

## APPENDIX IV.

## VITAMIN C.

The shortage of vitamin C in German occupied territory and the impossibility of importing sufficient cuantities, made it desirable to manufacture vitamin C in Holland. As Hoffmann-la-Roche were unwilling to grant a licence a new process was evolved. This starts from glucose and uses the classical steps :-

sorbitol - sorbose - ketogulonic acid.

It avoids the use of potassium-permanganate and of large cuantities of acetone, both substances having been very scarce in German-occupied countries. As an oxidizing agent sodium-chlorate is used. The conversion of sodium-ketogulonate to ascorbic acid is performed with the aid of sodium fluoride. The whole process falls outside the scope of the Swiss patents, although this is still being contested by Hoffman-la-Roche.

The yields of ascorbic acid are considerably inferior to those obtained by the Swiss process. The Dutch Government has stimulated research through an official organisation and they too have found a new process ("which, to our mind, is partly dependent on the Swiss patents").* Large scale production has also been taken up following this "Government-process".

* Dr. Tausk's comment.

## APPENDIX V.

## VITAMIN A.

In the course of experiments on a synthesis of Vitamin A the ketone I was prepared. From this substance the methyl-ester of Vitamin A-acid II is obtained by means of methyl-bromo-acetate and zinc in benzene.

This acid possessed about one-tenth of the biological activity of vitamin A itself.

The prospects for the preparation of Vitamin A from I are good. As ester of the iso-vitamin A acid II was also prepared. This substance was not active.

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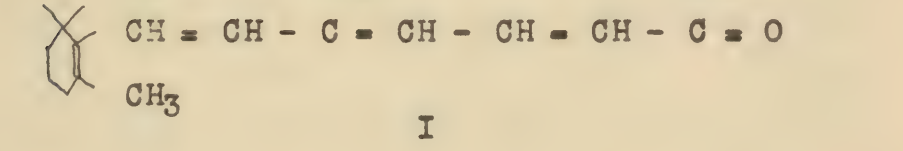

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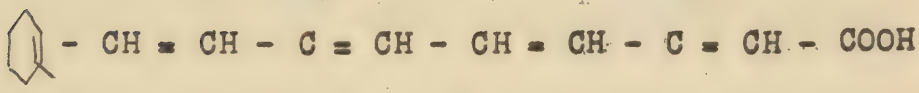

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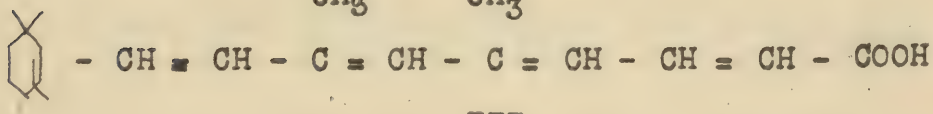

III

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## APPENDIX VI.

### MARFANIL $H_2N-H_2C-\langle\rangle-SO_2NH_2$

Marfanil (originally named Mesudin) was synthesized by Klarer. On the basis of experiments with animals it was recommended by Domagk for the clinical treatment of infections by anaerobic bacteria (e,g. gasgangrene). In the animal the toleration is excellent. (Domagk und Hegler, "Chemotherapie bakterieller Infektionen" 2. Aufl., Leipsiz 1942).

According to Hegler there is as yet (1942) little experience concerning the application in man. However, several investigators have recommended the preparation, amongst others Konjetzny, who used a combination with sulphanilamide (Prontalbin) locally against wound infection. This combination Marfanil-Prontalbin (1 part M, 9 parts P) is supposed to be active both against streptococci (and staphylococci) and anaerobics. The first publication concerning this combination is probably that by Beyer "Die Chemotherapie in der Hand des Chirurgen. Marfanil-Prontalbin, ein neues Wundantiseptikum" (Zbl.Chir. 68, 1730, 1941; not available in Oss).

Other References :-

Meuli. "Zur Frage der Frühbehandlung von Kriegsverletzungen mit Sulfonamiden". (Schweiz.med.Wschr. 74, 23, 1944). M. mentions that Klages (Med.Klin.1943, 37/38) saw good results in war wounds with Marfanil for the treatment and prophylaxis of gasgangrene. It is stated further that the combination Marfanil-Prontalbin has been recommended for war wounds by Domagk, Haferland, Konjetzny and others (in local and oral application).

Kirschner is sceptic about the benefit of M.P. in the treatment of wounds.

Flörcken stresses the harmlessness of large doses of M.P. powder, locally applied.

G.Herrmann, Marfanil-Prontalbinpuder in der Kriegschirurgie (Münch.med,Wschr. 90, 697 (1943), No. 48/49). H. reports on his experiences with the German army in Russia. He used the preparation for many different injuries. According to this author the locally applied M.P. powder gives a chance of success in fresh wounds only (up to 12 hours after the injury). As to fresh wounds, H. advocates universal application of M.P. powder (after primary wound excision).

H. W. Voigt (Sulphonamides in surgery). (Dtsch. med. Wschr. 70, 93 (1944) No. 7/8). V. used, among other preparations, M.P. powder locally with very favourable results.

R. Krueger "Sulphonamide an der Front." (Dtsch. med. Wschr. 69, 417 (1943) No. 21/22. K. saw good effects of sulphonamides (locally and orally) in the treatment of war wounds. He also mentions casually the use of M.P.

Eunike. "Uber die lokale Anwendung des Marfanil-Prontalbin in der Chirirgie zur Bekämpfung der Wundinfektion". Fortschritte der Therapie 18, 11 (1942) (not available in Oss).

Preparation of Marfanil:-

Formula $H_2N-H_2C-C_6H_4-SO_2NH_2$

German Patent 726386 (priority 27.1.39):

Protection for the reaction $RCH_2C_6H_4SO_2NH_2 \rightarrow NH_2CH_2C_6H_4SO_2NH_2$, executed in practically every imaginable way. (R= a substituent which can be converted to the amino group). Included is also the reduction of $N{\equiv}C-C_6H_4-SO_2NH_2$.

German Patent Application I 67614 (priority 8.8.40):

Halogenation of compounds with the formula $CH_3C_6H_4SO_2Hlg$ (Hlg = halogen) with halogenating agents at increased temperatures.

German Patent Application I 67629 (priority 8.8.40):

Reaction of compounds with the formula $HlgCH_2C_6H_4SO_2Hlg$ (as produced by the preceding patent application) with ammonia at temperature below 60°C, thus producing $HlgCH_2C_6H_4SO_2NH_2$

TIBATIN (I.G. Farben).

Formula $O_5H_{12}C_6{=}N-C_6H_4-SO_2-C_6H_4-N{=}C_6H_{12}O_5$
(digalactoside of diaminodiphenyl sulfone)

No particulars about the preparation available.

German Patent 694679 (priority 21.10.38):

Preparation of stable solutions of compounds like Tibatin, by addition of sugars to the solution. In an example the addition of inverted lactose to a solution of Tibatin is mentioned.

## APPENDIX VII

## DOLANTIN.

Chlorhydrate of 1-methyl-4-phenylpiperidin-4-carbonicacid-ethyl-ester. Tabl. 25 mg, amp. 100 mg.

No information was available at Organon regarding the manufacture of Dolantin. The following references to its use had been filed in the Organon scientific library :-

Schlungbaum (Med.Klin. 35, 1259, 1939).

Dolantin causes no addiction, no habituation.

Skamnakis (Zbl.Gynäk. 67, 1397, 1943).

Dolantin is frequently used in obstetrics as an analgesic. The author has recently replaced Dolantin by the "Analgeticum 446" bayer, the latter having a better spasmolytic and analgesic action (no details on the latter preparation).

v. Brücke (Wien.klin.Wschr. 1940 II, 854; ref Klin. Wschr. 20, 59, 1941).

Dolantin gives rise to addiction in predisposed individuals; therefore one has to be cautious in prescribing this preparation.

Kucher. "Zwei Fälle von Dolantinsucht" (Klin.Wschr. 19, 688, 1940).

Describes two cases of pronounced addiction (high doses; up to 25 amp. = 2,5 g pro die!). This should be a warning, as most clinicians deny that there can be such a thing as addiction to Dolantin. The author emphasizes the importance of this "ersatz" for morphine, the necessary raw material being available in Germany.

Garratal et al. (ref. Schweiz.med.Wschr. 73, 83,1943).

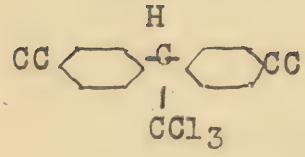
Prolonged use of Dolantin leads to habituation.

Oelkers and Wanowius (Klin.Wschr. 21, 752, 1942) demonstrated in mice an increase of toxicity of various substances, among which Dolantin, when the animals were treated with sulphonamides. This might be important for therapeutics in man.

APPENDIX VIII

WA-4200 2

GESAROL.



The drug is a poison for all kinds of insects. It works by simply contact with the animal. It is scarcely soluble in water but to a large extent in lipoid solvents. Therefore, it is easily absorbed by the lipoids in the cuticula of insects. It reaches the nerve endings and because it is a typical nerve poison kills the animals under violent spasms. The skin of mammals is not permeable for Gesarol, therefore no toxic effects are to be expected in these animals. Because contact with the skin is necessary, Gesarol is more active against flies, mosquitos, moths, etc. than against hairy animals like caterpillars.

It can best be applied by making a solution, e.g. in carbontetrachloride, and spraying this on the walls of the room, on the floor, on leaves of plants, etc. Very small amounts suffice, a stable could be kept free from flies for five to six weeks with an amount of five to seven γ pro $cm^2$.

To kill a rat of about 60 grams an amount of 25 mg given orally is necessary, mice of about 20 grams body weight can be killed with 20 mg.

The effect is not immediate, a lag time (for resorption) is present, depending on the species of animal.

A good survey of Gesarol and related drugs can be found in Helv.chim.acta. 27, 892, (1944).

## APPENDIX IX



## PENICILLIN

The Organon specialists knew nothing of any large scale manufacture of penicillin in Germany. It will of course be known in England, that Ciba of Bâle has taken up the manufacture of this product. Reports were published in a special issue of the Schweiz. Med. Wschr. 74, No.23, (1944).

From private information they know that Schering were engaged on rather intensive research on penicillin. On various occasions they obtained strains of penicillium notatum from Professor Westerdijk of Baarn, who is in charge of the "Centraal Bureau voor Schimmelcultures", having at its disposal what is probably the largest collection of moulds of the world. From discussions with Professor Westerdijk the impression was gathered that the strains of penicillium notatum, available in Holland and delivered to Schering, were probably inactive as regards penicillin-formation. It is understood that the fluid of their cultures is blue.

On the other hand Professor Julius, collaborating with Dr. Tausk of Organon and with Professor Westerdijk, took up penicillin research secretly. This has never been brought to the notice of the German wartime managers of Organon. A strain of moulds was found, giving a high yield of a very active anti-bacterial substance. It cannot yet be said whether this is identical with penicillin, although in many respects it behaved exactly like it.

Other Dutch centres of research have recently become actively interested in penicillin and other anti-bacterial substances of moulds. It is believed that none has got so far as Professor Julius and his collaborators.

## APPENDIX X.

### List of Shortages

(alphabetically arranged)

Acetic Acid: Delivery almost stopped after the Amsterdam factory had been damaged. In 1944 we received three tank loads from Germany.

Acetone: First years of the war almost unobtainable. Later on a special permit.

Acetylsalicylic Acid: Limited import from Germany in bulk.

Ethyl Alcohol: Though rather scarce always obtainable.

Aneurine: Irregular though sufficient deliveries from Germany and Hungary.

Asbestos Filters: (Seitz). Almost unobtainable.

Benzaldehyde: Sporadic supplies.

Boron Compounds unobtainable. The last batches of ampoules received from Germany were of boronfree glass of very poor cuality.

Chinydron: Very difficult. Chromium salts had to be handed in exchange(I.G.).

Chloroform: Very limited.

Chloro-sulphonic Acid: Obtainable though restricted.

Chromic Acid: Very short.

Codein: Not available.

Cod liver oil: Unobtainable.

Coffeine and its salts: Not available in Germany. Small stocks in Holland. Germans attempted a synthesis.

| | |
|---|---|
| Dichloro-ethylene: | In Holland unobtainable. I.G. Farben delivered small quantities but informed us just before the liberation that they were unable to continue. |
| Dimethylsulphate: | Unobtainable. |
| Glass Apparatus: | Orders for laboratory glass-ware delivered after several years or not at all. Particularly funnels ar unobtainable. |
| Glycerine: | Though liable to restrictions, available in modest quantities. |
| Iodine: | Compounds very scarce. |
| Iron Ammonium Citrate: | Almost unobtainable. |
| Manganese sulphate: | Not available. |
| Papaine: | Unobtainable. |
| Papavarine: | Delivered only once. |
| Peanut Oil: | Completely exhausted. |
| Phenacetin: | Unobtainable. |
| Potassium Permanganate: | Not available. |
| Raney metal: | After the bombing of the factory, unobtainable. |
| Sodium Benzoate: | Supplied in small quantities. |
| Sodium Fluoride: | Not available. |
| Sulphuric Acid: | Decreasing delivery. |
| Semicarbazide: | We have the impression that the last stocks are exhausted. |
| Tartaric Acid: | Unobtainable. |
| Trichloro-acetic Acid: | Not available. |

All fine chemicals for analytical purposes were very difficult to obtain, or were not delivered at all.